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The Patent Office

17 June 1992

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-2JUL'91#003C1774 PAT 1 77 UC 15.00

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Notes

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The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

❶ Title of invention

1 Please give the title of the invention: MEDICAMENTS

❷ Applicant's details

☐ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name: SMITHKLINE BEECHAM PLC

Country *(and State of incorporation, if appropriate)*: UNITED KINGDOM

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases**, please give the following details:

Address: SB HOUSE
GREAT WEST ROAD
BRENTFORD
MIDDLESEX

UK postcode *(if applicable)*: TW8 9BD

Country: UNITED KINGDOM

ADP number *(if known)*: 5791553001 pa

2d, 2e and 2f: If there are further applicants please provide details on a separate sheet of paper.

☐ **Second applicant** ***(if any)***

2d If you are applying as a corporate body please give:

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❸ An address for service in the United Kingdom must be supplied

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❸ Address for service details

3a Have you appointed an agent to deal with your application?

Yes [x] No [ ] ➡ ***go to 3b***

⬇ ***please give details below***

Agent's name JULIA FLORENCE

Agent's address CORPORATE PATENTS
SMITHKLINE BEECHAM
MUNDELLS
WELWYN GARDEN CITY
HERTFORDSHIRE

Postcode AL7 1EY

Agent's ADP number 447123100 2

3b: If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

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④ Reference number

Agent's or applicant's reference number *(if applicable)*

JF/P30104

⑤ Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ ***go to 6***

⬇

please give details below

❑ number of earlier application or patent number

❑ filing date

(day month year)

❑ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

⑥ Declaration of priority

⑥ If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day, month, year)*

❼ *The answer must be 'N*
- *any applicant is not an inventor*
- *there is an inventor who is not an applicant, or*
- *any applicant is a corporate body.*

❼ Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inve

Please mark correct box

Yes ☐ No ☒ ➡ ***A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

❽ *Please supply duplicates of claim(s), abstract, description and drawing(s).*

❽ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			-
Claim(s)	-	Description	14
Abstract		Drawing(s)	-

8b Which of the following documents also accompanies the application?

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Priority documents *(please state how many)*	
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Patents Form 10/77 – Request for Substantive Examination	

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Signed Julia Florence Date 25 (day) 06 (month) 91 (year)

JULIA FLORENCE

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MEDICAMENTS

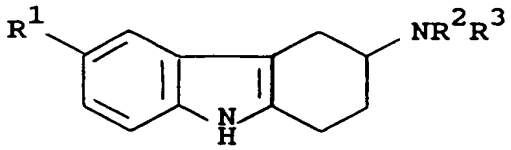
The present invention relates to certain tetrahydrocarbazole derivatives for use in the treatment of disorders characterised by excessive vasodilatation, in particular the treatment of migraine.

Migraine is a non-lethal disease suffered by one in ten individuals. The main symptom is headache; other symptoms include vomiting and photophobia. Currently, the most widely used treatment for migraine involves administration of ergotamine, dihydroergotamine or methysergide, which are also used prophylactically. All these drugs are agonists of $5HT_1$-like receptors. However, such treatment is associated with a number of adverse side effects. In addition, some patients experience a "withdrawal headache" following the cessation of treatment with an ergot product, such as ergotamine, causing them to repeat the treatment and resulting in a form of addiction.

In view of the foregoing, there is clearly a need for the provision of effective and safe medicaments for the treatment of migraine.

It has now been found that certain tetrahydrocarbazoles are agonists at $5HT_1$-like receptors and are expected to have utility in the treatment of migraine.

The present invention therefore provides the use of compounds of general formula (I):



(I)

wherein :

R^1 represents hydrogen, halogen, cyano, hydroxy, C_{1-6}alkoxy, arylC_{1-6}alkoxy, $-CO_2R^4$, $-(CH_2)_nCONR^5R^6$ or $-(CH_2)_nSO_2NR^5R^6$;
R^4 represents hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;
R^5 and R^6 each independently represent hydrogen or C_{1-6}alkyl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a ring;
n represents 0, 1 or 2; and
R^2 and R^3 each independently represent hydrogen or C_{1-6}alkyl;
and physiologically acceptable salts thereof, in the manufacture of a medicament for the treatment or prophylaxis of migraine.

It will be appreciated that compounds of formula (I) may contain one or more assymetric centres, and such compounds will exist as optical isomers (enantiomers). The invention thus includes all such enantiomers and mixtures, including racemic mixtures, thereof.

In the compounds of formula (I) a halogen atom may be a fluorine, chlorine, bromine or iodine atom. An alkyl group or moiety may have a straight or branched chain. Suitable aryl groups include for example unsaturated monocyclic or bicyclic rings and partially

saturated bicyclic rings of up to 12 carbon atoms, such as phenyl, naphthyl and tetrahydronaphthyl. When R^5 and R^6 together with the nitrogen atom form a ring, this is preferably a 5 to 7-membered saturated heterocyclic ring, which may optionally contain a further heteroatom selected from oxygen, sulphur or nitrogen. Suitable rings thus include pyrrolidino, piperidino, piperazino and morpholino.

In the above compounds R^1 preferably represents a group $-(CH_2)_n CONR^5R^6$ wherein n represents 0 and R^5 and R^6 each represent hydrogen.

R^2 and R^3 each preferably represent hydrogen.

R^4 preferably represents C_{1-6}alkyl.

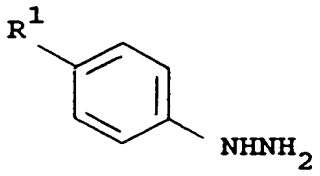
Suitable physiologically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts such as those formed with inorganic acids e.g. hydrochloric, sulphuric or phosphoric acids and organic acids e.g. oxalic, succinic, maleic, acetic or fumaric acid.

A particularly preferred compound for use according to the present invention is 3-amino-1,2,3,4-tetrahydrocarbazole-6-carboxamide. This is believed to be a novel compound and as such, forms a further aspect of this invention.

The invention also provides a process for the preparation of novel compounds of formula (I).

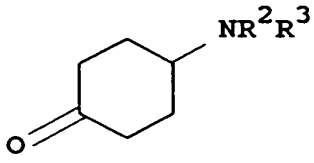
Compounds of formula (I) may be prepared by methods known in the art for the preparation of tetrahydrocarbazoles, for example :

A) Reaction of a compound of formula (II) :



(II)

(wherein R^1 is as hereinbefore defined) or an acid addition salt thereof with a compound of formula (III) :



(III)

(wherein R^2 and R^3 are as hereinbefore defined) or an N-protected derivative thereof; or

B) Conversion of one compound of formula (I) into another compound of formula (I) eg.

(i) to prepare a compound of formula (I) wherein R^1 represents $-CONH_2$ or CO_2R^4, hydrolysis of a compound of formula (I) wherein R^1 represents cyano, or an N-protected derivative thereof;

(ii) to prepare a compound of formula (I) wherein R^1 represents $-CONR^5R^6$, amination of a compound of formula (I) wherein R^1 represents $-CO_2H$, or an

N-protected derivative thereof; or

(iii) to prepare a compound of formula (I) wherein one of R^2 and R^3 is hydrogen and the other is C_{1-6}alkyl, alkylation of a compound (I) in which R^2 and R^3 are both hydrogen;

(iv) to prepare a compound of formula (I) wherein R^1 represents hydroxy, cleavage of a compound wherein R^1 represents alkoxy or aralkoxy;

followed if necessary by deprotection of any protected nitrogen atoms and if desired by salt formation.

Process (A), which is a form of the Fischer indole synthesis, may be carried out using methods well known in the art. Thus, the reaction may be effected in a solvent, for example an alcohol such as ethanol or butanol; or acetic acid, and at a temperature in the range 0 to 100°C.

Hydrazines of formula (II), which are usually employed as the hydrochloride salt, are known compounds, or may be prepared by conventional methods.

A cyclohexanone of formula (III) may be prepared by oxidation of the corresponding cyclic alcohol, using an oxidising agent such as pyridinium chlorochromate, pyridinium dichromate, dipyridine Cr (VI) oxide or manganese dioxide.

It is well known in the chemical art that hydrolysis of a nitrile initially results in an amide, which can be further hydrolysed to an acid. It will therefore be appreciated that the precise product of process (Bi) will depend upon the reaction conditions chosen for the

hydrolysis. To obtain a compound wherein R^1 represents H_2NCO- the hydrolysis is preferably effected using hydrogen peroxide in the presence of an alkali hydroxide e.g. sodium hydroxide, in a solvent such as an alcohol e.g. methanol. Other suitable means of hydrolysis include acetic acid and BF_3; or formic acid and hydrobromic or hydrochloric acid. To prepare a compound wherein R^1 represents -COOH acid or base catalysed hydrolysis may be used.

Process (Bii) may be effected by reacting a compound of formula (I) wherein R^1 is $-CO_2H$ with an amine HNR^5R^6, in the presence of a coupling agent e.g. dicyclohexylcarbodiimide or N,N'-carbonyldiimidazole. Alternatively the carboxylic acid starting material may first be reacted to form an activated derivative of the carboxyl group, for example an acid chloride, acid anhydride or activated ester, which is then reacted directly with an amine HNR^5R^6.

Alkylation according to process (Biii) may be effected by reacting the amine of formula (I) with an acylating agent, for example an anhydride, such as acetic or propionic anhydride, to form an intermediate in which one of R^2 or R^3 is $-C(O)C_{1-6}$alkyl, followed by reduction of said intermediate to give the desired product. Other reagents and conditions will be apparent to those skilled in the art.

Cleavage according to process (Biv) may be effected by reduction, using methods well known in the art.

It will be appreciated that in many of the above reactions it will be necessary to protect the group $-NR^2R^3$ when one or both of the groups R^2 and R^3 represent hydrogen. Suitable N- protecting groups are

well-known in the art and include for example acyl groups such as acetyl, trifluoroacetyl, benzoyl, methoxycarbonyl, benzyloxycarbonyl or phthaloyl; and aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl. When R^2 and R^3 both represent hydrogen the nitrogen atom is preferably protected as the phthalimide. The protecting groups should be easily removable at the end of the reaction sequence. N-deprotection may be effected by conventional methods, for example a phthaloyl group may be removed by reaction with hydrazine; an acyl group such as benzoyl may be cleaved by hydrolysis and an aralkyl group such as benzyl may be cleaved by hydrogenolysis.

Compounds of formula (I) have been found to be agonists at $5HT_1$-like receptors and are expected to have utility in the treatment and/or prophylaxis of migraine, and other conditions associated with cephalic pain.

In a further aspect therefore the present invention provides a compound of formula (I) or a physiologically acceptable salt thereof for use in therapy, in particular for the treatment and/or prophylaxis of migraine, and other conditions associated with cephalic pain.

In a still further aspect, the invention provides a method of treatment of migraine which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a physiologically acceptable salt thereof.

The present invention also provides the use of a compound of formula (I) or a physiologically acceptable salt thereof in the manufacture of a medicament for the treatment and/or prophylaxis of migraine.

In therapeutic use, the compounds of the present invention are usually administered as a standard pharmaceutical composition.

The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof and a physiologically acceptable carrier.

The compounds of formula (I) and their physiologically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or

suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base.

The physiologically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

BIOLOGICAL DATA

5-HT_1-like Receptor Screen

Dog Saphenous Vein

Helicoids of dog saphenous vein were set up at 37°C in modified Krebs solution at a resting force of 10 mN. The solution also contained 1 µmol/l each of ketanserin prazosin, atropine and mepyramine, 6 µmol/l cocaine and 200 µmol/l ascorbate. Nearly isomeric contractions were measured with force transducers on a polygraph. The tissues were exposed twice to 5-hydroxytryptamine (5-HT) 2 µmol/l followed by washes. A cumulative concentration-effect curve was determined, followed by a curve to 5-HT in the presence of the highest used concentration of test compound. Contractions caused by the test compound were compared with those caused by 5-HT. The intrinsic activity of the test compound was calculated as the ratio of the maximum test compound-induced effect over the effect caused by 2 µmol/l 5-HT. The EC_{50} of the test compound was estimated from the corresponding effect curve. When appropriate equilibrium dissociation constants Kp were estimated by the method of Marano & Kaumann (1976, J. Pharmacol. Exp. Ther. 198, 518-525).

In this screen the compound of Example 1 had an EC_{50} of 0.07 µM.

Example 1

3-Amino-6-cyano-1,2,3,4-tetrahydrocarbazole hydrochloride

A solution of 4-aminocyclohexanol hydrochloride (6.08 g, 0.04 mole) in water (60 ml) was brought to pH 8 with aqueous sodium bicarbonate solution. N-carbethoxy-phthalimide (8.76 g, 0.04 mole) was added followed by tetrahydrofuran (until homogenous solution obtained). The clear solution was stirred at room temperature overnight. During this time a white solid was precipitated. The tetrahydrofuran was removed in vacuo and the remaining aqueous solution was extracted with ethyl acetate until the solution was clear. The ethyl acetate extracts were combined, washed with water, dried ($MgSO_4$) and concentrated to give 4-phthalimido cyclohexanol as a white solid (7.1 g).

A solution of 4-phthalimido cyclohexanol (7.1 g, 0.029 mole) in dichloromethane (250 ml) was treated with pyridinum chlorochromate (8.6 g, 0.04 mole) and the resulting dark mixture was stirred at room temperature overnight. Diethyl ether (50 ml) was added and the mixture filtered through keiselguhr. The filtrate was concentrated in vacuo and the residue purified by column chromatography (SiO_2; $CHCl_3$/EtOAc) to give 4-phthalimido cyclohexanone as a white solid (6.4 g).

4-Cyanophenyl hydrazine hydrochloride (4.41 g, 0.026 mole) was dissolved in acetic acid (100 ml) and sodium acetate (2 g) was added. 4-Phthalimido cyclohexanone (6.4 g, 0.026 mole) was added and the mixture heated under reflux overnight. The solvent was removed in vacuo and the residue triturated with methanol to give 3-phthalimido-6-cyano-1,2,3,4-tetrahydrocarbazole as a beige solid, (5.3 g).

A suspension of the above product (1 g) in ethanol (40 ml) was treated with hydrazine in water (10 ml). The reaction mixture was stirred at room temperature overnight during which time the reactants became dissolved. The solvent was removed in vacuo and the residue partitioned

between aqueous potassium carbonate and ethyl acetate. The ethyl acetate solution was washed with water, dried and concentrated in vacuo to give 3-amino-6-cyano-1,2,3,4-tetrahydrocarbazole as a beige solid (500 mg). This product was converted into the hydrochloride salt to give the title compound, mp 289°C (dec.).

^{1}H NMR [250 MHz, MeOD] $\underline{\delta}$ 1.98--2.18 (1H, m), 2.25-2.40 (1H, m), 2.77 (1H, dd), 2.98 (2H, m), 3.22 (1H, dd), 3.68 (1H, m), 7.34 (1H, d), 7.43 (1H, d), 7.82 (1H, s).

Example 2

3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride

The product of Example 1 (400 mg) was dissolved in tetrahydrofuran, and di-t-butyl dicarbonate (500 mg) was added. The mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the residue purified by column chromatography (SiO_2; $CHCl_3$/EtOAc) to give 3-t-butyloxycarbonylamino-6-cyano-1,2,3,4-tetrahydrocarbazole (40 mg).

A mixture of the above product nitrile (440 mg), aqueous hydrogen peroxide (30%, 0.5 ml) and sodium hydroxide (aq) (20%, 0.5 ml) in methanol (25 ml) was stirred at room temperature overnight. Sodium metabisulphate (100 mg) was added and the solvent removed in vacuo. The residue was dissolved in ethyl acetate and the ethyl acetate layer was removed, dried and concentrated in vacuo to give a gummy solid which was purified by column chromatography (SiO_2; $CHCl_3$/ EtOAc) to give 3-t-butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole as a white solid (400 mg).

The above product (400 mg, 0.0012 mole) was dissolved in dioxan (100 ml) and HCl gas was bubbled through the solution for 20 minutes. During this time a white solid was precipitated. Excess hydrogen chloride was swept from the solution by bubbling through N_2, and the solid product, 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole

hydrochloride was collected by filtration, washed with diethyl ether and dried to give the title compound as a white solid (300 mg).

^{1}H NMR [250 MHz, DMSO-d^6] $\underline{\delta}$ 1.96 (1H, m), 2.16-2.30 (1H, m), 2.74 (1H, dd), 2.85 (2H, m), 3.12 (1H, dd), 1 signal obscured by H_2O at ca. 3.6, 7.08 (1H, brd.s), 7.27 (1H, d), 7.61 (1H, d), 7.87 (1H, brd.s), 7.99 (1H, s), 8.39 (3H, brd.s).

Example 3

3-Amino-6-methoxy-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 4-methoxyphenyl hydrazine hydrochloride (0.87g, 5.0 mmol) with 4-phthalimido-cyclohexanone (1.22g, 5.0 mmol) in ethanol (20 ml) heated under reflux for 2 hr, followed by cooling and removal of the precipitated solid by filtration gave 3-phthalimido-6-methoxy-1,2,3,4-tetrahydrocarbazole (1.62g).

The above product (1.57g, 4.5 mmol) was suspended in ethanol (100 ml) and treated with hydrazine hydrate (23 ml) while stirring at room temperature. After 30 min, the solvent was removed in vacuo and the residue was partitioned between K_2CO_3 (aq) and EtOAc. The latter layer was separated, washed with water, dried ($MgSO_4$) and evaporated to dryness. This residue was dissolved in ethanol and treated with ethereal HCl until cloudy, then left to stand overnight to yield the title compound (0.95g) mp > 250°C. ^{1}H NMR [250 MHz, DMSO-d^6] $\underline{\delta}$ 1.81-2.02 (1H, m), 2.10-2.28 (1H, m), 2.65 (1H, dd), 2.82 (2H, m), 3.02 (1H, dd), 1 signal obscured by H_2O at ca. 3.5, 3.74 (3H, s), 6.66 (1H, d), 6.84 (1H, d), 7.14 (1H, d), 8.16 (3H, brd.s).

Example 4

3-Amino-6-bromo-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 4-bromophenylhydrazine hydrochloride (4.0g, 18.1 mmol) with 4-phthalimido-cyclohexanone (4.39g, 18.1 mmol) in refluxing n-butanol for 20 min, followed by

cooling, filtration, and evaporation of the filtrate to dryness yielded 3-phthalimido-6-bromo-1,2,3,4-tetrahydrocarbazole as an orange solid (7.45g).

This product (0.33g, 0.83 mmol) was suspended in EtOH (13 ml) and treated with hydrazine hydrate (3 ml), then left to stir at room temperature overnight. The solid precipitate was filtered off, and the filtrate was evaporated to dryness and partitioned between K_2CO_3 (aq) and EtOAc. After separation of the organic layer, washing with water, drying (Mg SO_4) and evaporation to dryness, the residue was dissolved in MeOH and treated with HCl gas. Solvent was removed in vacuo and the residue was crystallized from ethanol/ethyl acetate to yield the title compound as a cream-coloured solid (0.15g), mp 308-310°C. ^{1}H NMR [250 MHz, DMSO-d^6] $\underline{\delta}$ 1.91 (1H, m), 2.10-2.26 (1H, m) 2.63 (1H, dd), 2.84 (2H, m), 3.04 (1H, dd), 3.50 (1H, m), 7.12 (1H, d), 7.24 (1H, d), 7.55 (1H, s), 8.15 (2H, brd.s), 11.12 (1H, s).